



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/62, A61K 48/00, A01K 67/027	A2	(11) International Publication Number: WO 99/50425 (43) International Publication Date: 7 October 1999 (07.10.99)
(21) International Application Number: PCT/US99/06799 (22) International Filing Date: 30 March 1999 (30.03.99) (30) Priority Data: 60/079,831 30 March 1998 (30.03.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US Not furnished (CIP) Filed on Not furnished (71) Applicant (for all designated States except US): BAYLOR COLLEGE OF MEDICINE [US/US]; One Baylor Plaza, Houston, TX 77030 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SPENCER, David, M. [US/US]; 810 Marston Street, Houston, TX 77019 (US). SLAWIN, Kevin, M. [US/US]; 6560 Fannin Street, Houston, TX 77030 (US). (74) Agents: KOCH, Robert, J. et al.; Fulbright & Jaworski L.L.P., 801 Pennsylvania Avenue, Washington, DC 20004-2604 (US).		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: REGULATED APOPTOSIS USING CHEMICALLY INDUCED DIMERIZATION OF APOPTOSIS FACTORS		
(57) Abstract <p>The present invention discloses artificial death switches (ADSs) based on chemically induced dimerization of the cysteine proteases, caspase-1 (ICE) and caspase-3 (YAMA). In both cases, aggregation of the target protein is achieved by a non-toxic, lipid-permeable, dimeric FK506 analog that binds to an attached FK506-binding protein (FKBP). The intracellular crosslinking of caspase-1 or caspase-3 is sufficient to trigger rapid apoptosis in a Bcl-x_L-independent manner, suggesting that these conditional pro-apoptotic molecules can bypass intracellular checkpoint genes, like Bcl-x_L, that limit apoptosis. Since these chimeric molecules are derived from autologous proteins, they should be non-immunogenic and thus ideal for long-lived gene therapy vectors. These properties should also make chemically-induced apoptosis (CIA) useful for developmental studies, for treating hyperproliferative disorders and for developing animal models to a wide variety of diseases.</p>		

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(54) Title: REGULATED APOPTOSIS USING CHEMICALLY INDUCED DIMERIZATION OF APOPTOSIS FACTORS		
(57) Abstract <p>The present invention discloses artificial death switches (ADSs) based on chemically induced dimerization of the cysteine proteases, caspase-1 (ICE) and caspase-3 (YAMA). In both cases, aggregation of the target protein is achieved by a non-toxic, lipid-permeable, dimeric FK506 analog that binds to an attached FK506-binding protein (FKBP). The intracellular crosslinking of caspase-1 or caspase-3 is sufficient to trigger rapid apoptosis in a Bcl-x_L-independent manner, suggesting that these conditional pro-apoptotic molecules can bypass intracellular checkpoint genes, like Bcl-x_L, that limit apoptosis. Since these chimeric molecules are derived from autologous proteins, they should be non-immunogenic and thus ideal for long-lived gene therapy vectors. These properties should also make chemically-induced apoptosis (CIA) useful for developmental studies, for treating hyperproliferative disorders and for developing animal models to a wide variety of diseases.</p>		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06799

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 A61K48/00 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 20463 A (GEN HOSPITAL CORP) 12 June 1997 (1997-06-12) page 3, line 17 -page 11, line 34 page 39 -page 53; example 2 ---	1-27
X	MUZIO ET AL: "AN INDUCED PROXIMITY MODEL FOR CASPASE-8 ACTIVATION" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, 30 January 1998 (1998-01-30), pages 2926-2930, XP002116597 the whole document ---	1-27
A	HENKART ET AL: "ICE FAMILY PROTEASES: MEDIATORS OF ALL APOPTOTIC CELL DEATH?" IMMUNITY, vol. 4, 1996, pages 195-201, XP002116598 cited in the application the whole document ---	
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 September 1999

Date of mailing of the international search report

12/10/1999

Name and mailing address of the ISA

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Sitch, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 02684 A (UNIV LELAND STANFORD JUNIOR ;HARVARD COLLEGE (US)) 26 January 1995 (1995-01-26) cited in the application page 3, line 18 -page 12, line 32 ----	
A	WO 97 31898 A (ARIAD GENE THERAPEUTICS INC ;HOLT DENNIS A (US); KEENAN TERENCE P) 4 September 1997 (1997-09-04) page 2, line 5 -page 3, line 15 page 41, line 10 - line 30 page 85, line 20 - line 31 page 101, line 24 -page 103, line 39 ----	
A	WO 97 31611 A (CHIRON CORP) 4 September 1997 (1997-09-04) page 3, line 18 -page 4, line 34 ----	13,14, 23,24
P,X	MACCORKLE ET AL: "SYNTHETIC ACTIVATION OF CASPASES: ARTIFICIAL DEATH SWITCHES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, USA, vol. 95, 31 March 1998 (1998-03-31), pages 3655-3660, XP002116599 the whole document ----	1-27
P,X	SLAWIN ET AL: "APOPTOSIS-INDUCTION IN BPH-DERIVED SMOOTH MUSCLE CELLS: PRECLINICAL STUDIES OF A NOVEL GENE THERAPEUTIC APPROACH TO BPH" JOURNAL OF UROLOGY, vol. 159, May 1998 (1998-05), page 110 XP002116600 abstract 423 -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/06799

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-16 completely and 17-26 partially (insofar as such relate to in vivo methods) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06799

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9720463	A	12-06-1997	NONE	
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